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Treatment of uterine sarcoma

A survey of 49 patients

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Abstract *Purpose:* Surgery, radiotherapy and chemotherapy are employed in the treatment of uterine sarcoma. We claim to evaluate the role of radiotherapy in the treatment of uterine sarcoma. *Patients and methods:* We report a retrospective study of 49 patients with uterine sarcoma treated from 1990–1999 at Masaryk Memorial Cancer Institute in Brno. All 49 patients had surgery, 19 (38.7%) had adjuvant radiotherapy and 25 (51%) had chemotherapy. Using the FIGO classification: 71.4% had stage I, 6.1% stage II, 16.3%, stage III and 6.1% stage IVa disease. 42.9% of tumors were mixed Müllerian tumors, 34.7% leiomyosarcomas and 22.4% endometrial stromal sarcomas. 12 cases (24.5%) had a local recurrence, 7 (14.3%) had hematogenous dissemination. There was an increased disease free interval (DFI) for patients treated with adjuvant radiotherapy (p=0.005). The DFI was favourably influenced by the stage of the disease. Of 12 patients with a local recurrence only one had postoperative radiotherapy. Radiotherapy had an impact on overall survival (OS). The five-year OS probability was 51.6% without radiotherapy and 88.9% with radiotherapy (p=0.0066). *Conclusion:* We conclude that postoperative radiotherapy in our series of patients diagnosed with uterine sarcoma has an impact on locoregional and disease-free progression intervals (LRFI, DFI) and overall survival (OS). The most important prognostic factor is the extend of the disease (stage). Stage I patients have a significantly better survival.

Keywords Uterine sarcoma · Radiotherapy · Survival · Disease-free interval · Local recurrence

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Introduction

Uterine sarcoma (US) represents 1–3% of all gynecological and 2–5% of all uterine malignancies. Sarcoma has a poor prognosis. The 5-year survival for patients with stage I disease is between 50–70%, and 0–20% for the remaining stages. The extremely agressive behaviour of uterine sarcoma leads to an early-pattern of local recurrence and then widespread dissemination. These characteristics make uterine sarcoma one of the most malignant of all uterine tumors.

The most common sarcomas are: mixed Müllerian sarcoma (MMS or mixed mesodermal sarcoma) (50%), leiomyosarcoma (LMS) (30%) and endometrial stromal sarcoma (ESS) (15%).

The most common presenting symptoms are vaginal bleeding and pain. Curettage of the uterus followed by histologic examination are diagnostic. Frequently the diagnosis is made histologically after surgery for uterine myoma. The rarity of uterine sarcoma and its pathological heterogenity have made these tumors difficult to study in large numbers.

Radical surgery is the primary form of treatment. Up to now the role of adjuvant radiotherapy has not been clearly established. Although the impact of radiotherapy is accepted on survival, for local disease control, few benefits were reported. This report assesses retrospectively the impact of radiotherapy on local control and survival in uterine sarcoma.

Patients and methods

Between 1990 and 1999, 49 patients were treated by surgery at the Masaryk Memorial Cancer Institute in Brno for uterine sarcoma.

Adjuvant external beam radiotherapy was administered to 19 cases (38.7%), adjuvant chemotherapy 25 cases (51%) and 11 patients (22.4%) had combined radiotherapy and chemotherapy.

We excluded 8 inoperable patients. 41 patients had a total abdominal hysterectomy and 4 patients with low grade endometrial stromal sarcoma had a modified radical hysterectomy.

Radiotherapy patients were treated with 18 MV fotons from a linear accelerator using four fields (box-technique). External

Table 1 Treatment

Treatment	Number of pts	[%]
Surgery	49	100.0
Radiotherapy	19	38.8
Chemotherapy	25	51.0

Table 2 Histology variants

Histology variant	No of pts	[%]
Mixed Mullerian malignant tumor/MMMT/	21	42.9
Leiomyosarcoma LMS	17	34.7
Endometrial stromal sarcoma ESS	11	22.4

Table 3 Stage and tumor

Stage	MMT	LMS	ESS	Total
I	13 (26.5%)	12 (24.5%)	10 (20.4%)	35 (71.4%)
II	1 (2%)	2 (4.1%)		3 (6.1%)
III	5 (10.2%)	2 (4.1%)	1 (2%)	8 (16.3%)
IV	2 (4.1%)	1 (2%)		3 (6.1%)

ESS endometrial stromal sarcoma, *LMS* leiomyosarcoma, *MMT* mixed Mullerian tumor

beam radiotherapy was given in 2.0 Gy daily doses. The mean total dose was 50 Gy with a range from 44–56 Gy. Radiation was combined with intracavitary vaginal Cesium-137 in 4 patients. In all four cases the dose was 20 Gy at 0.5 cm from the vaginal epithelium. Twenty-five patients (51%) had chemotherapy alone and eleven patients (22.4%) had radiotherapy and chemotherapy. Most often chemotherapeutic regimes were CYVADIC (cyclophosphamid+ vincristin+ adriamycin+ dakarbazin) and VAC combination (vincristin+ actinomycin D + cyclophosphamid) (Table 1, 2, 3).

We related histology, stage of disease and radiotherapy to local control and overall survival.

The Kalpan-Meier test and SPSS were used for this purpose.

Results

The mean age of our patients was 55.8 years (range 23–77) at the time of diagnosis. The mean age of the patients with mixed mesodermal sarcoma was higher at 65.5 years. 21 patients (42.9%) had a mixed Müllerian tumor, 17 patients (34.7%) had a leiomyosarcoma and 11 patients (22.4%) had an endometrial stromal sarcoma (Table 2).

The stages were distributed as follows: There were 35 patients (71.4%) with stage I disease, three (6.1%) with stage II, eight (16.3%) with stage III and three (6.1%) with stage IV disease (Table 3).

The mean time of follow-up was 42.7 months (range 4–123), with a median of 28 months.

During the study, 12 patients (24.5%) had a local recurrence at a mean interval of 7.6 months (range 1–16) with a median of 5.5 months. The impact of radiotherapy on local recurrence was unambiguous; only one of the patients with a local recurrence had postoperative radiotherapy.

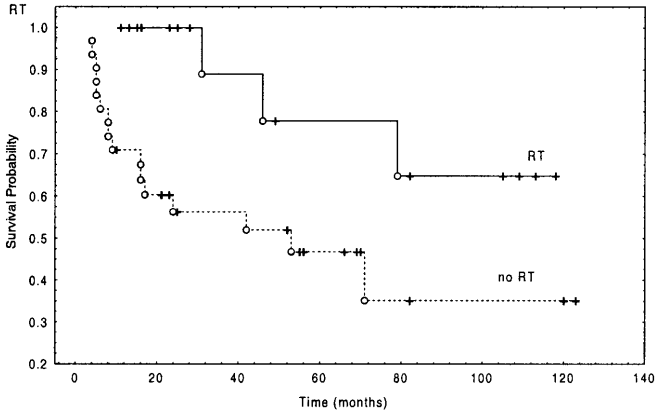

Fig. 1 Kaplan-Meier estimates of the impact of radiotherapy on disease free interval

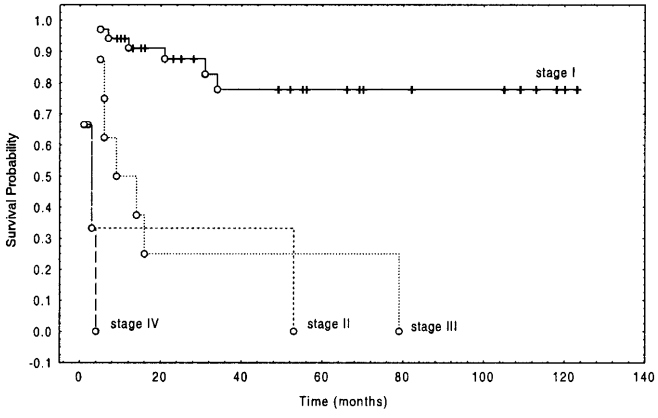

Fig. 2 Kaplan-Meier estimates of the disease-free interval at various stages of disease

Distant metastases occurred in 7 patients (14.3%), and 4 of them also had a local recurrence.

49% of patients had a two-year disease-free interval. The probability of a disease-free interval was 57.9% at 2 years. Figure 1 shows the impact of radiotherapy on the disease-free interval (p=0.005) and Fig. 2 the impact of stage on the same interval.

The overall 1- and 2-year survival for patients who did not have radiotherapy was 51.6% and it was 88.9% for patients who had radiotherapy. The figure was 65% for all patients.

The impact of radiotherapy on overall survival is shown in Fig. 3 and the relation between stages of disease and overall survival in Fig. 4. The survival for patients with stage I disease is significantly higher when compared to other stages (p<0.0005).

Our patients with endometrial stromal sarcoma had a better overall survival than patients with other histological variants (Fig. 5). This difference was on the border of statistical significance (p=0.056). Table 4 compares our results with some of those previously published.

Table 4 Comparison of our results with some of those previously published

Author	No of patients	pts. given post-operative RT	Stage [%]				Histology [%]			Local recurrence [%]	Distant mts [%]	Overall survival		Disease-free interval	
			I	II	III	IV	LMS	ESS	MMMS			2 year	5 year	2 year	5 year
Our results	49	19 (38.7%)	71.4	6.1	16.3	6.1	34.7	22.4	42.9	24.5	14.3	75.5	65	49	24.5
Ferrer et al. [5] (GOCO) 1999	103	54 (52%)	64	15.5	11.5	9	41.5	16.5	39	44.6	30.1	63.7	56	52.9	48.7
Nola et al. [14] 1996	80	65 (81.2%)	65.4		34.6		38.7	32.5	28.7						
Chauveinc et al. [2] 1999	73		83.5	6.8		10.9	44	19	31	25.7	48.6		45		
Coquard et al. [3] 1997	29	29 (100%)	62.1	17.2	10.3	10.3	37.9	20.7	41.4	24.1	27.6	66	57	54	50
Jereczek et al. [9] 1996	42	17 (40.5%)	57.1	7.1	16.6	19	35.7	30.9	33.3	45.2	21.4	54	30		
Fait et al. [4] 1998	39	13 (33%)					58.9	17.9	17.9				36		

LMS leiomyosarcoma, *ESS* endometrial stromal sarcoma, *MMMT* mixed Mullerian malignant tumor

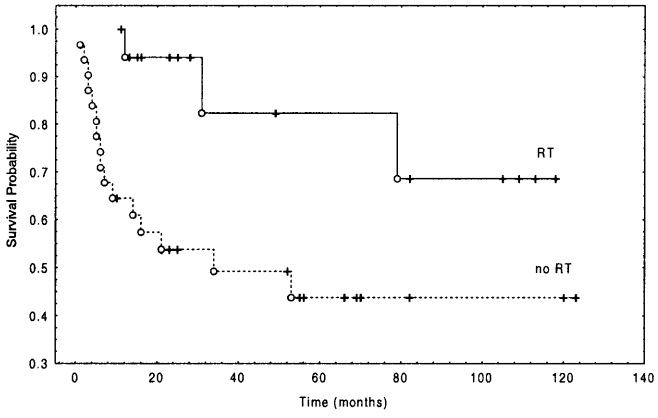

Fig. 3 Kaplan-Meier estimates of influence of radiotherapy on overall survival

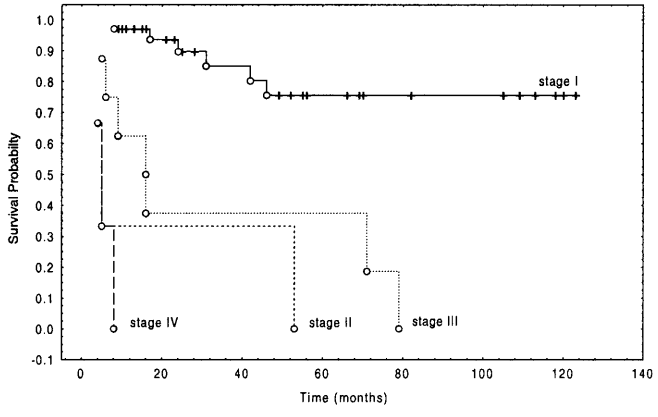

Fig. 4 Kaplan-Meier estimates of the impact of stage of disease on overall survival

Discussion

Uterine sarcomas are extremely aggressive with early dissemination and local recurrence. The mean age at

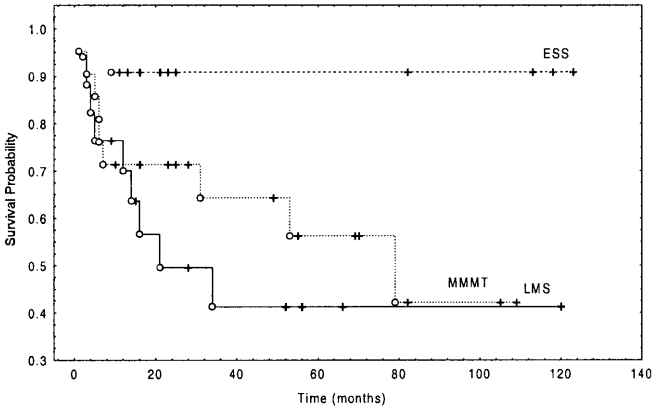

Fig. 5 Kaplan-Meier estimates of survival among the patients with different sarcomas. *ESS* endometrial stromal sarcoma, *MMMT* mixed Mûllerian malignant tumor, *LMS* leiomyosacoma

diagnosis for mixed mesodermal tumors has been given as 58 years [6, 18].

In our study it was 65.5 years in patients with MMT. The stage of disease is one of the most important prognostic factors [10, 14, 18]. 50% of tumors are confined to the uterus (stage I) at the time of diagnosis [18]. 71% of our patients were stage I. Our 2-year survival in stage I patients was 82.8%, in other stages 28.6%. Some, but not all [14] studies claim better overall survival in patients with endometrial stromal sarcoma [1, 18]. The survival of our patients with endometrial stromal sarcoma was just statistically significantly better than the survival figures for those with other tumors. It is because we had many patients with stage I endometrial sarcoma. Radical surgery (mainly total abdominal hysterectomy and bilateral salpingo-oophorectomy) is the mainstay of treatment in uterine sarcoma. Surgery includes peritoneal lavage and omental biopsy or omentectomy. Simple hysterectomy may be the correct treatment in young patients with low-grade endometrial sarcoma. We had 4 such patients who survived with no evidence of recurrent disease.

The role of postoperative radiotherapy in the management of uterine sarcoma is still controversial. It undoubtedy prevents some local recurrences. The incidence of pelvic recurrence appears to be higher than the incidence of hematologic dissemination. In our study distant recurrence was diagnosed in 14.5% and local recurrence in 24.5% of patients. French studies have produced similar results [2, 3]. Ferrero [5] and Polish authors [9] noted a 40% incidence of local recurrence. Of the 12 patients with recurrence in our study, only one had had postoperative radiotherapy. Sarcomas, generally regarded as radioresistant tumors, need higher doses of radiation. Mean dose of 50–60 Gy over 5–6 weeks given to the pelvis by external beam is recommended. A four field technique is the most appropriate and most common. Some authors recommend external beam therapy and brachytherapy in combination [6, 8, 18] and Larson describes better local effect and overall survival in stage I patients with Mullerian sarcoma given combined therapy [12]. The impact of radiotherapy on overall survival is not clear; some authors [3, 5, 18] claim a beneficial effect and others do not confirm this [6, 10]. Our patients who were given postoperative radiotherapy had a significantly higher overall survival rate when compared with those not irradiated postoperatively. 2-year and 5-year actuarial overall survival figures for all patients were 73.5% and 26.5% respectively.

In similar studies 2-year actuarial overall survival varied between 54–66% [3, 4, 5, 9]. We had many of low-stage patients in our study and this would lead to a higher overall survival (Table 4). Multicentre prospective trials will be needed to asses the exact impact of radiotherapy on overall survival. Our study could not be used to evaluate the role of chemotherapy because of the heterogenity of the regimens used.

Conclusion

Uterine sarcomas belong among gynekologic malignancies with poor prognosis despite their low incidence. The extent of the disease at the time of diagnosis is the main prognostic factor. Stage I patients show significantly higher survival than other stage patients in our trial. We conclude that postoperative radiotherapy in our series of patients diagnosed with uterine sarcoma has had an impact on locoregional and disease-free progression interval and overall survival.

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